Blood coagulation as a biochemical sytem

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19 84

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BLOOD COAGULATION AS A BIOCHEMICAL SYSTEM.

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Systems theory in biochemistry can simply be considered to be an extension of enzyme kinetics.

Classical enzyme kinetics describes so called linear systems. That means systems in which there is a monotonous relation between concentrations and velocities. If the concentration of an enzyme or a substrate increases the reaction velocity will increase, if the concentration of an inhibitor increases the reaction velocity will decrease etc. Linearity does not mean that there is a rectilinear relationship between concentration and velocity but it does indicate that velocity is monotonously and continuously dependent upon the concentrations of the effectants.

Classical enzyme kinetics calculates variations in the concentrations of reactants on basis of the law of mass action and assumptions on the chemical reaction mechanisms involved.

The best known and simplest example is the interaction between enzyme and substrate:

$$E + S \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} C \xrightarrow{k_{+2}} E + P$$

in which each of the arrows indicates a reaction, the velocity of which is calculated by means of the law of mass action:

$$\frac{dC}{dt} = v_{+1} - (v_{-1} + v_{+2}) = k_{+1} \cdot E_{free} \cdot S_{free} - (k_{-1} + k_{+2})\, C$$

$$\frac{dP}{dt} = k_{+2} \cdot C$$

Already this simple set of differential equations cannot be solved by classical mathematical means and additional assumptions are necessary to arrive at analytical solutions.

One of these, the steady state assumption that leads to classical Michaelis Menten kinetics, is particularly important not only because the whole of classical enzyme kinetics is based upon it but also because it illustrates that in a chemical system not only reaction velocities are dependent upon concentrations but also concentrations are dependent upon reaction velocities. Because the breakdown of the enzyme substrate complex is dependent upon its concentration, that concentration (C) will rise until the breakdown velocity of C approximately equals its velocity of formation and $dC/dt \approx 0$; hence the concentration C is determined by the reaction constants and the concentrations of E and S. This approximation holds from shortly after the start of the reaction and during the time that the initial reaction velocity is maintained, i.e. in the domain of classical Michaelis Menten kinetics.

If one wants to describe in general mathematical terms what happens in any biochemical system the above can serve as an example. The system can be completely described by a set of differential equations that relate the reaction velocities, that is the rate of change of concentration in time (dC/dt), to reaction constants and concentrations.

Now the difference between systems theory and classical kinetics is only in the degree of complication of the differential equations. It will be clear that where the very simple case described above already cannot be solved by classical mathematical analysis without making extra assumptions, the more complicated systems have to be approached by numerical analysis, i.e. by the use of computer methods. This again explains why the development of systems theory goes in parallel with the development of computer theory and technology.

If the set of equations arrives at a certain degree of complexity the solutions, i.e. the relationships between velocity and concentration, acquire nonlinear properties. This means to say that the relations between velocities and concentrations not necessarily remain continuous and monotonous.

The "catastrophy theory" as developed by Thom and Zeeman is a mathematical theory that describes such nonlinear systems.

In these systems there are three variables, the independent variable (X), e.g. a concentration, the dependent variable (Y), e.g. a reaction velocity and a modifying variable (A) e.g. the concentration of

a modifier of the reaction properties, e.g. an inhibitor or activator. Such systems may show the following, nonlinear, properties.

a) Exitation thresholds, i.e. depending upon the value of A, a small increase of X will cause a sudden jumplike change in Y.

b) Multiple states. To a given value of X two distinct values of Y may exist at a fixed value of A. This property leads to the following one:

c) Memory. Which of two possible values of Y at a fixed value of A will be actually present in a given system may be dependent on whether X approached its present value from higher or from lower values.

d) Delay. A disturbance of the system if persisting for a short time may allow it to return to its pre-existant state, a slightly longer or more important disturbance may cause the system to change to another state (see b).

e) Cyclic behaviour. If the modifying variable A is coupled to the dependent variable Y (A = f(Y)) time dependent cyclic changes of the concentration of one or more reactants may be produced.

f) Chaotic behaviour. Only slightly more complicated systems than those showing cyclic behaviour will show such complicated time dependent changes that a cycle can no longer be recognised.

g) Morphogenesis. Apart from the purely chemical systems described that are usually considered to be well stirred ("random flow conditions") and hence homogeneous in space, one may consider unstirred systems in which transport of reaction components by diffusion becomes one of the phenomena to be considered. It has been shown that in such systems inhomogeneties may arise spontaneously.

The models become even more complicated if non random flow conditions are imposed upon it, as is the case in blood vessels in the living organism. In very general terms it may be stated that those systems that give rise to cyclic behaviour in well stirred systems will show regular patterns if diffusion is allowed to play its role, chaotic systems will cause irregular spatial patterns.

It will not have escaped the attention of the reader that many of the properties of the coagulation system are those of a nonlinear system. Exitation thresholds, multiple states, delay and irregular morphogenesis can all be recognised.

Is the reaction mechanism of coagulation sufficiently complicated to account for this nonlinear behaviour ? Nobody will be surprised that it is. The russian investigator Sel'kov has made a study of the different biochemical mechanisms that explain nonlinear behaviour. One of these fits the reaction mechanism of thrombin formation:

Where IIase stands for prothrombinase and the positive and negative feedback is caused by the effect of thrombin on this enzyme complex. As thrombin activates factor V it promotes its own formation, but as it also inactivates factor Va via its activating action upon protein C, the system becomes sufficiently complicated to show nonlinear behaviour.

The interplay of positive and negative feedback systems in coagulation is extremely fascinating. Thrombin activates factor VIII and inactivates it as well. Thrombin (together with collagen) activates platelets by making them expose their procoagulant phospholipids. An excess of phospholipids inhibits thrombin formation as well as factor X activation etc. etc.

From the above it will be clear that systems theory in biochemistry may serve to grasp the complex behaviour of complex systems. In the authors opinion it will hardly help in the analysis of these systems though. If the coagulation system is seen as a black box, its input-output relations will hardly tell us anything except that the interior exceeds a certain degree of complexity.

In fact the authors have been paying attention to the possibilities offered to coagulation kinetics by systems theory ever since 1968. Together with adequate mathematicians and physicists they have tried to apply this theory to the kinetic analysis of the coagulation system. To sum up more than a decennium's experience it must be said that systems theory may be useful only in understanding the complex behaviour of the system once the biochemical analysis of the system has succeeded to describe the system in enough detail. If this is not the case, systems theory can only serve to discard hypotheses that are oversimplifying.

There is a simple and discouraging reason behind this. Nonlinear systems are always so complicated as to involve more than about a dozen reaction constants. A biochemical analysis of a system

requires determination of reaction constants. Filling a dozen constants to the input-output relations of a biochemical "black-box" is possible but will not guarantee any resemblance of the mathematical mechanism proposed for the black-box with the biochemical mechanism really present.

In the course of the years it has become our conviction that biochemical analysis by isolation and characterization of the functional subsystems is the souvereign way to understanding the mechanism of coagulation. System theory may serve to understand the nonlinear behaviour of the reconstituted subsystems afterwards.

Because of the subject of this lecture being somewhat outside the scope of haemostasiology we will give only a few general references (1, 2, 3).

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